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| FORM PTO-1449 <u>INFORMATION DISCLOSURE STATEMENT</u> | | ATTY. DOCKET NO. 0609.4280001 | APPLICATION NO. 08/896,053 | |
| | | APPLICANT JANSSENS <i>et al.</i> | | |
| | | FILING DATE July 17, 1997 | GROUP 1808 | |

U.S. PATENT DOCUMENTS

| EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
|---------------------|-----|-----------------|------------|------------------------|-------|-----------|-------------|
| <i>ANP62</i> | AA1 | 5,485,827 | 01/23/1996 | Zapol <i>et al.</i> | | | 02/10/1995 |
| | AB1 | 5,498,539 | 03/12/1996 | Harrison <i>et al.</i> | | | 07/02/1992 |
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| | AL | | | | | | Yes No |
| | AM | | | | | | Yes No |
| | AN | | | | | | Yes No |
| | AO | | | | | | Yes No |
| | AP | | | | | | Yes No |

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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| <i>ANP62</i> | AR | 1 | Adnot, S., <i>et al.</i> , "Loss of Endothelium-dependent Relaxant Activity in the Pulmonary Circulation of Rats Exposed to Chronic Hypoxia," <i>J. Clin. Invest.</i> 87:155-162 (1991). |
| | AS | 1 | Assender, J.W., <i>et al.</i> , "Does Nitric Oxide Inhibit Smooth Muscle Proliferation?," <i>J. Cardiovasc. Pharmacol.</i> 17(Suppl. 3):S104-S107 (1991). |
| | AT | 1 | Bernstein, A., <i>et al.</i> , "Gene Transfer with Retrovirus Vectors," in: <i>Genetic Engineering: Principles and Methods</i> , Volume 7, Setlow, J.K., and Hollaender, A., eds., Plenum Press; New York, pp. 235-261 (1985). |

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| EXAMINER | <i>ANP62</i> | DATE CONSIDERED | <i>9/18/98</i> |
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| <i>PHS</i> | AR | 2 | Bredt, D.S., <i>et al.</i> , "Localization of nitric oxide synthase indicating a neural role for nitric oxide," <i>Nature</i> 347:768-770 (1990). | | | | |
| <i>J</i> | AS | 2 | Cline, M.J., "Perspectives for Gene Therapy: Inserting New Genetic Information into Mammalian Cells by Physical Techniques and Viral Vectors," <i>Pharmac. Ther.</i> 29:69-92 (1985). | | | | |
| <i>V</i> | AT | 2 | Cohen, A.H., <i>et al.</i> , "Inhibition of Cyclic 3'-5'-Guanosine Monophosphate-specific Phosphodiesterase Selectively Vasodilates the Pulmonary Circulation in Chronically Hypoxic Rats," <i>J. Clin. Invest.</i> 97(1):172-179 (January 1996). | | | | |

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| EXAMINER | <i>DR. S. M.</i> | DATE CONSIDERED | <i>01/18/98</i> |
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|  | AR | 3 | de Graaf, J.C., <i>et al.</i> , "Nitric Oxide Functions as an Inhibitor of Platelet Adhesion Under Flow Conditions," <i>Circulation</i> 85:2284-2290 (1992). | | | | |
|  | AS | 3 | Dick, J.E., <i>et al.</i> , "Genetic manipulation of hematopoietic stem cells with retrovirus vectors," <i>Trends in Genetics</i> 2:165-170 (1986). | | | | |
|  | AT | 3 | Frostell, C.G., <i>et al.</i> , "Inhaled Nitric Oxide Selectively Reverses Human Hypoxic Pulmonary Vasoconstriction without Causing Systemic Vasodilation," <i>Anesthesiology</i> 78(3):427-435 (1993). | | | | |

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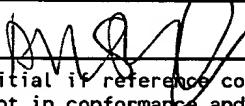
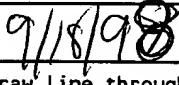
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|  | AR | 4 | Furchtgott, R.F., and Vanhoutte, P.M., "Endothelium-derived relaxing and contracting factors," FASEB J. 3:2007-2018 (1989). |
|  | AS | 4 | Garg, U.C., and Hassid, A., "Nitric Oxide-generating Vasodilators and 8-Bromo-Cyclic Guanosine Monophosphate Inhibit Mitogenesis and Proliferation of Cultured Rat Vascular Smooth Muscle Cells," J. Clin. Invest. 83:1774-1777 (1989). |
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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| <i>PNB</i> | AR | 5 | Girard, C., <i>et al.</i> , "Inhaled Nitric Oxide after Mitral Valve Replacement in Patients with Chronic Pulmonary Artery Hypertension," <i>Anesthesiology</i> 77:880-883 (1992). |
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| <i>✓</i> | AT | 5 | Hazinski, T.A., <i>et al.</i> , "Localization and Induced Expression of Fusion Genes in the Rat Lung," <i>Am. J. Respir. Cell Mol. Biol.</i> 4:206-209 (1991). |

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| EXAMINER | <i>DMSN</i> | DATE CONSIDERED |
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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| <i>DRS</i> | AR | <u>6</u> | Heath, D., "The pathology of pulmonary hypertension," <i>Eur. Respir. Rev.</i> 3(16):555-558 (1993). |
| <i>V</i> | AS | <u>6</u> | Hibbs, J.B., Jr., <i>et al.</i> , "Nitric Oxide: A Cytotoxic Activated Macrophage Effector Molecule," <i>Biochem. Biophys. Res. Comm.</i> 157(1):87-94 (1988). |
| <i>V</i> | AT | <u>6</u> | Ignarro, L.J., "Endothelium-derived nitric oxide: actions and properties," <i>FASEB J.</i> 3:31-36 (1989). |

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| <i>SPB</i> | AR | 7 | Janssens, S.P., <i>et al.</i> , "Cloning and Expression of a cDNA Encoding Human Endothelium-derived Relaxing Factor/Nitric Oxide Synthase," <i>J. Biol. Chem.</i> 267(21):14519-14522 (1992). |
| <i>SPB</i> | AS | 7 | Janssens, S.P., <i>et al.</i> , "Functional and structural changes with hypoxia in pulmonary circulation of spontaneously hypertensive rats," <i>J. Applied Physiol.</i> 77(3):1101-1107 (1994). |
| <i>SPB</i> | AT | 7 | Janssens, S.P., <i>et al.</i> , "Adenoviral-mediated Transfer of the Human Endothelial Nitric Oxide Synthase Gene Reduces Acute Hypoxic Pulmonary Vasoconstriction in Rats," <i>J. Clin. Invest.</i> 98(2):317-324 (July 1996). |

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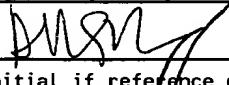
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| | | | |
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|  | AR | 8 | Johns, R.A., <i>et al.</i> , "Endothelium-Dependent Relaxation and Cyclic GMP Accumulation in Rabbit Pulmonary Artery Are Selectively Impaired by Moderate Hypoxia," <i>Circ. Res.</i> 65:1508-1515 (1989). |
|  | AS | 8 | Kawai, N., <i>et al.</i> , "Constitutive endothelial nitric oxide synthase gene expression is regulated during lung development," <i>Am. J. Physiol.</i> 268:L589-L595 (April 1995). |
|  | AT | 8 | Kiem, H.-P., <i>et al.</i> , "Gene therapy and bone marrow transplantation," <i>Curr. Opin. Oncol.</i> 7(2):107-114 (March 1995). |

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| <i>PNB</i> | AR | 9 | Lowenstein, C.J., <i>et al.</i> , "Cloned and expressed macrophage nitric oxide synthase contrasts with the brain enzyme," <i>Proc. Natl. Acad. Sci. USA</i> 89:6711-6715 (1992). |
| <i>J</i> | AS | 9 | Marletta, M.A., "Nitric oxide: biosynthesis and biological significance," <i>Trends Biochem. Sci.</i> 14:488-492 (1989). |
| <i>J</i> | AT | 9 | McQuillan, L.P., <i>et al.</i> , "Hypoxia inhibits expression of eNOS via transcriptional and posttranscriptional mechanisms," <i>Am. J. Physiol.</i> 267:H1921-H1927 (1994). |

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| <i>MSB</i> | AR | <u>10</u> | Miller, A.D., "Human gene therapy comes of age," <i>Nature</i> 357:455-460 (1992). |
| <i>J</i> | AS | <u>10</u> | Moncada, S., <i>et al.</i> , "Nitric Oxide: Physiology, Pathophysiology, and Pharmacology," <i>Pharmacol. Rev.</i> 43:109-142 (1991). |
| <i>J</i> | AT | <u>10</u> | Morrow, J.F., "The Prospects for Gene Therapy in Humans," <i>Ann. N.Y. Acad. Sci.</i> 265:13-21 (1976). |

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| | | APPLICANT JANSSENS <i>et al.</i> | |
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| | AL | | | | | | Yes No |
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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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| <i>BSB</i> | AR | 11 | Nathan, C., "Nitric oxide as a secretory product of mammalian cells," <i>FASEB J.</i> 6:3051-3064 (1992). |
| <i>J</i> | AS | 11 | Pepke-Zaba, J., <i>et al.</i> , "Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension," <i>Lancet</i> 338:1173-1174 (1991). |
| <i>J</i> | AT | 11 | Radomski, M.W., <i>et al.</i> , "The Role of Nitric Oxide and cGMP in Platelet Adhesion to Vascular Endothelium," <i>Biochem. Biophys. Res. Comm.</i> 148(3):1482-1489 (1987). |

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| <i>DRB</i> | AR | <u>12</u> | Rimar, S., and Gillis, N.C., "Selective Pulmonary Vasodilation by Inhaled Nitric Oxide Is Due to Hemoglobin Inactivation," <i>Circulation</i> 88(6):2884-2887 (1993). |
| <i>↓</i> | AS | <u>12</u> | Roberts, J.D., <i>et al.</i> , "Inhaled nitric oxide in persistent pulmonary hypertension of the newborn," <i>Lancet</i> 340:818-819 (1992). |
| <i>↓</i> | AT | <u>12</u> | Roberts, J.D., Jr., <i>et al.</i> , "Continuous Nitric Oxide Inhalation Reduces Pulmonary Arterial Structural Changes, Right Ventricular Hypertrophy, and Growth Retardation in the Hypoxic Newborn Rat," <i>Circ. Res.</i> 76(2):215-222 (February 1995). |

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| <i>DRS</i> | AR | <u>13</u> | Rossaint, R., et al., "Inhaled Nitric Oxide for the Adult Respiratory Distress Syndrome," <i>N. Engl. J. Med.</i> 328(6):399-405 (1993). |
| <i>DRS</i> | AS | <u>13</u> | Salser, W., et al., "Gene Therapy Techniques: Use of Drug Resistance Selections in Intact Animals to Insert Human Globin Genes Into Bone-Marrow Cells of Living Mice," in: <i>Organization and Expression of Globin Genes</i> , Stamatoyannopoulos, G., and Nienhuis, A.W., eds., Alan R. Liss, Inc., pub., New York, N.Y., p. 313-334 (1981). |
| | AT | <u>13</u> | A copy of the original paper must be included Setoguchi, Y., et al., "Transfer of endothelial nitric oxide synthase gene in the purpose of gene therapy for pulmonary arterial hypertension," <i>Nippon Rinsho Jap. J. Clin. Med.</i> 54(2):369-76 (February 1996), English language abstract, Medline database accession no. 96435198. |

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| <i>DMS</i> | AR | <u>14</u> | Shaul, P.W., <i>et al.</i> , "Acute and Prolonged Hypoxia Attenuate Endothelial Nitric Oxide Production in Rat Pulmonary Arteries by Different Mechanisms," <i>J. Cardiovasc. Pharmacol.</i> 22:819-827 (1993). |
| <i>✓</i> | AS | <u>14</u> | Stribling, R., <i>et al.</i> , "Aerosol gene delivery <i>in vivo</i> ," <i>Proc. Natl. Acad. Sci. USA</i> 89:11277-11281 (1992). |
| <i>✓</i> | AT | <u>14</u> | Stuehr, D.J., and Griffith, O.W., "Mammalian Nitric Oxide Synthases," <i>Adv. Enzymol. Relat. Areas Mol. Biol.</i> 65:287-346 (1992). |

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| <i>DRS</i> | AR | 15 | Must Submit an actual copy of the paper Tzeng, E., <i>et al.</i> , "Vascular gene transfer of the human inducible nitric oxide synthase: characterization of activity and effects on myointimal hyperplasia," <i>Mol. Med.</i> 2(2):211-225 (March 1996), abstract, Medline database accession no. 96295016. |
| <i>DRS</i> | AS | 15 | Vanhoutte, P.M., "The Endothelium - Modulator of Vascular Smooth-Muscle Tone," <i>N. Engl. J. Med.</i> 319:512-513 (1988). |
| <i>DRS</i> | AT | 15 | von der Leyen, H.E., <i>et al.</i> , "Gene therapy inhibiting neointimal vascular lesion: <i>In vivo</i> transfer of endothelial cell nitric oxide synthase gene," <i>Proc. Natl. Acad. Sci. USA</i> 92:1137-1141 (February 1995). |

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| <i>AB</i> | AR | 16 | Xue, C., et al., "Distribution of NOS in normoxic vs. hypoxic rat lung: upregulation of NOS by chronic hypoxia," Amer. J. Physiol. 267:L667-L678 (1994). |
| | AS | | |
| | AT | | |

EXAMINER *AB* DATE CONSIDERED 9/18/98

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